P970043/S7

Summary of Safety and Effectiveness Data
For a Supplemental Premarket Approval Application

I. GENERAL INFORMATION

Device Generic Name: Ophthalmic Excimer Laser System

Device Trade Name: LADARVision® Excimer Laser System

Applicant's Name and Address: Summit Autonomous, Inc.
2800 Discovery Drive
Orlando, FL 32826

Date of Panel Recommendation: March 17, 2000

Premarket Approval Application (PMA) Number: P970043/S7

Date of Notice of Approval to Applicant: September 22, 2000

Expedited Review: Expedited review was granted on December 17, 1999 based on the potential public health benefit of providing a one-step approach to treating hyperopic astigmatism versus the two-step, off-label approach currently employed.

The LADARVision® Excimer Laser System was approved on November 2, 1998 for the indication of photorefractive keratectomy for the reduction or elimination of mild to moderate myopia of between –1.00 and –10.00 D sphere and less than or equal to –4.00 D astigmatism at the spectacle plane, the combination of which must result in an attempted correction of between –0.50 and –10.00 D spherical equivalent at the spectacle plane where the sphere or cylinder is at least 1.00 D (P970043). On May 9, 2000, the device was also approved for the indication of laser in-situ keratomileusis treatments for the reduction or elimination of myopia of less than –9.00D sphere and –0.50 to less than –3.00D of astigmatism at the spectacle plane (P970043/S5). The sponsor submitted the current supplement to further expand the indication statement. The updated pre-clinical and clinical work to support this expanded indication is provided in this summary. For more information on the data that supported the approved indications, the Summaries of Safety and Effectiveness Data to those PMA applications should be requested from the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20857. Please identify Docket OOM-1592 for the original PMA application (P970043) and OOM-1593 for supplement 5 (P970043/S5). The summaries can also be found on the FDA CDRH Internet Home Page located at http://www.fda.gov/cdrh/pmapage.html.

II. INDICATIONS FOR USE

The LADARVision Excimer Laser System is indicated for use:

- in Laser In-Situ Keratomileusis (LASIK) treatments for the reduction or elimination of refractive error of less than or equal to +6.00D of sphere and -6.00D of cylinder at the spectacle plane (hyperopia with or without astigmatism and mixed astigmatism);
- in subjects with documented stability of refraction for the prior 12 months, as demonstrated by a change of less than or equal to 0.50D for corrections up to +6.00D SE; and,
- in subjects who are 21 years of age or older.

III. CONTRAINDICATIONS

LASIK is contraindicated:

- in patients with signs of keratoconus;
- in pregnant or nursing women;
- in patients who are taking one or both of the following medications: isotretinoin (Accutane) or amiodarone hydrochloride (Cordarone); or,
- in patients with an autoimmune disease, collagen vascular disease, or an immunodeficiency disease.

IV. WARNINGS AND PRECAUTIONS

A. WARNINGS

See the labeling.

B. PRECAUTIONS

See the labeling.

V. DEVICE DESCRIPTION

The LADARVision Excimer Laser System (LADARVision) that is the subject of this supplement has the same ablation characteristics (e.g., fluence, pulse rate, repetition rate, shot algorithm, tracker function, etc.) as the previously approved

system, except that the shot patterns are different for the new indications. In the approved PRK/LASIK treatments of myopia, the shot pattern is densest at the center of the cornea to flatten the central curvature. In the treatment of hyperopia, the shot pattern is densest in a ring around the center of the cornea to steepen the central curvature. When astigmatism is present, the amounts of myopic or hyperopic correction are different along the major and minor axes. Mixed astigmatism occurs when the astigmatism is greater than the hyperopia, so the curvature must be steepened along one axis and flattened along the orthogonal axis.

The LASIK procedure requires the use of a commercially available microkeratome that has been cleared for marketing via premarket notification. The device used in this study consists of the head, a suction ring, handle, wrenches, shaft, motor, handpiece, disposable blades, and power supply with footswitches and power cords. The applanation lens set, tonometer, optical zone marker, spatula, and digital thickness gauge are provided as separate components which complete the system.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are currently several other alternatives for the treatment of spherical hyperopia, hyperopic astigmatism, and mixed astigmatism:

Contact Lenses
Laser Thermal Keratoplasty
Photorefractive Keratectomy (PRK)
Spectacles

Each alternative has its own advantages and disadvantages. A prospective patient should fully discuss with his/her eye care provider these alternatives in order to select the correction method that best meets his/her expectations and lifestyle.

VII. MARKETING HISTORY

The device has been marketed in 7 countries: USA, Canada, United Kingdom, Italy, Spain, Greece and Australia. The LADARVision has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse reactions associated with LASIK include: loss of best spectacle corrected visual acuity, worsening of patient complaints such as double vision, sensitivity to bright lights, increased difficulty with night vision, fluctuations in vision, increase in intraocular pressure, corneal haze, secondary surgical intervention, corneal infiltrate or ulcer, corneal epithelial defect, corneal edema,

problems associated with the flap including a lost, misplaced or misaligned flap, retinal detachment, and retinal vascular accidents.

The rates of these adverse reactions at the 1 month, 3 month, 6 month and 9 month visits are found in the Summary of Clinical Studies and in Table 24. Subjective symptoms at 6 months are reported in Table 25.

IX. SUMMARY OF PRECLINICAL STUDIES

The preclinical studies performed to support the new indications were ablation tests in polymethylmethacrylate to demonstrate that the device can create the shape required by each indication.

X. SUMMARY OF CLINICAL STUDIES

The sponsor performed a clinical study of the LADARVision in the US under the auspices of an investigational device exemptions application (IDE) G980137. The data from this study served as the basis for the approval decision. Specifically, safety and effectiveness outcomes at 6 months postoperative were assessed as stability was reached by that time. Outcomes at 9 months postoperatively were also evaluated for confirmation. Within the treatment range of the protocol, three types of hyperopia were being studied: hyperopic eyes with < -1 D of astigmatism which received treatment for spherical hyperopia only (spherical eyes), eyes with hyperopic refractive error present in one or both meridians (hyperopic astigmatic eyes), and eyes with hyperopic error in one meridian and myopic error along the orthogonal meridian (mixed astigmatic eyes). The IDE study is described in detail, with the data stratified by the type of hyperopia, as follows:

A. STUDY OBJECTIVES

The objective of this study was to determine the safety and effectiveness of the LADARVision for the correction of spherical hyperopia ≤ +6.0 D with or without astigmatism ≤ -6.0 D at the spectacle plane, where at least one component was 1.00 D or greater, using the LASIK procedure.

B. STUDY DESIGN

The study was prospective, non-randomized, unmasked, and multi-center, where the primary control was the preoperative state of the treated eye *(i.e.,* comparison of pretreatment and post-treatment visual parameters in the same eye).

C. INCLUSION AND EXCLUSION CRITERIA

Enrollment in the LASIK study was limited to patients with: spherical hyperopia ≤ +6.0 D with or without astigmatism ≤ -6.0 D at the spectacle plane, and where at least one component was 1.00 D or greater; documented stability of refraction for the prior 12 months, as demonstrated by a change of less than or equal to 0.50 D; at least 18 years of age; at least 20/40 in both eyes; and, manifest and cycloplegic refractions did not differ by more than 1.00 D in either the sphere or cylinder component.

Patients were not permitted to enroll in the LASIK study if they met any of the following exclusion criteria: history of or clinically active or visually significant ocular disease or pathology; corneal scars within the ablation zone or other corneal abnormality such as recurrent erosion; progressive or unstable myopia or keratoconus; irregular corneal astigmatism; previous intraocular or corneal surgery; history of herpes keratitis; autoimmune disease, connective tissue disease, clinically significant atopic syndrome or insulin dependent diabetes; use of chronic systemic corticosteroids or other immunosuppressive therapy; pregnant or nursing; use of ophthalmic medications other than artificial tears for treatment of an ocular pathology; severe dry syndrome unresolved by treatment; allergy to study medications; glaucoma or glaucoma filtering surgery; participation in another ophthalmic clinical trial; at risk for angle closure; and at risk for developing strabismus post-treatment.

D. STUDY PLAN, PATIENT ASSESSMENTS, AND EFFICACY CRITERIA

All subjects were expected to return for follow-up at 1 day, 1 week, and 1, 3, 6, 9,12, 18 and 24 months postoperatively.

Bilateral simultaneous treatments and retreatments were approved on January 7, 1999. Subjects were permitted to have their fellow eyes treated on the same day as the primary eye or any time thereafter provided there were no active adverse reactions for the primary eye.

Retreatments were allowed after the 3-month follow-up visit and on the approval of the Medical Director. To be retreated for undercorrection, all of the following conditions had to be met:

a) UCVA worse than 20/25 or residual hyperopia greater than or equal to 0.75D;
b) stable refraction, with MRSE on the two most recent consecutive visits 1 month apart within 0.50D for eyes whose primary treatment was an attempted correction up to 6D and within 1D for attempted corrections higher than 6D;

c) stable UCVA, i.e., within one line on two consecutive visits at least 1 month apart;
d) patients signed a separate informed consent document, wherein they were informed of their increased risk associated with retreatment;
e) the eligibility criteria were met and an ophthalmic evaluation (including VA, manifest refraction and slit lamp) was done to establish the preoperative condition of the eye; and,
f) prior written approval was obtained from the sponsor of the study.

Retreatment of hyperopic eyes for overcorrection was allowed if the UCVA was worse than 20/25 or induced myopia was greater than or equal to 0.75D at the two most recent consecutive visits one month apart. All other conditions listed above must also have been met.

Retreatment for the purpose of correcting residual refractive error was not considered a treatment failure. Results of retreated eyes were analyzed separately from the primary cohort.

No other ocular surgery procedures were allowed unless deemed medically necessary by the investigator. The sponsor had to be notified prior to any secondary surgical interventions, except in the case of an emergency.

In the event of a miscreated flap with the microkeratome, which was an adverse reaction in the study, a second cut with the microkeratome may be performed and the laser ablation procedure may be completed after a minimum of 3 months. Approval from the Medical Monitor was required prior to treating an eye with a miscreated flap.

Preoperatively, the subjects' medical and ocular histories were recorded. The objective parameters measured during the study included: uncorrected visual acuity, best spectacle corrected visual acuity, pupil size, manifest and cycloplegic refraction, intraocular pressure, and status of the cornea, conjunctiva, anterior chamber, lens, vitreous, retina, and externals. These parameters were collected preoperatively and only as needed postoperatively: gonioscopy and pachymetry. Corneal topography was assessed preoperatively and postoperatively at specific follow-ups; however, data was used only to evaluate anomalous results. A patient questionnaire was administered to subjects preoperatively and at 3, 6, and 12 months postoperatively. Specular microscopy and contrast sensitivity were performed in subgroups of patients.

The primary efficacy variables for this study were improvement of UCVA based on the pre-treatment goal of the procedure and predictability of manifest refraction.

E. STUDY PERIOD, INVESTIGATIONAL SITES, AND DEMOGRAPHICS

1. Study Period and Investigational Sites

Subjects were treated between August 10, 1998 and June 4, 1999. The database for this PMA supplement reflected data collected through March 22, 2000 and included 360 eyes: 152 spherical eyes, 143 hyperopic astigmatic eyes, and 65 mixed astigmatic eyes. There were 6 investigational sites with 7 lasers and 15 investigators.

2. Demographics

The demographics of this study population are typical of a contemporary refractive surgery trial performed in the US. The cohort consists primarily of Caucasians. Preoperative patient characteristics that were found to associate with outcomes are discussed in section X.F.2.f.

Table 1: DEMOGRAPHICS

	Spherical Eyes (N=152)	Hyperopic Astigmatic Eyes (N=143)	Mixed Astigmatic Eyes (N=65)
Gender			
Female	87 (57.2%)	74 (51.7%)	16 (24.6%)
Male	65 (42.8%)	69 (48.3%)	49 (75.4%)
Race			
Caucasian	151 (99.3%)	139 (97.2%)	65 (100%)
Hispanic	1 (0.7%)	4 (2.8%)	0
Asian	0	0	0
Black	0	0	0
Eye			
Left	80 (52.6%)	67 (46.9%)	30 (46.2%)
Right	72 (47.4%)	76 (53.1%)	35 (53.8%)
Age (Years)			
Average	56.5	52.8	46.6
Standard Deviation	6.9	11.3	9.1
Minimum	38	21	31
Maximum	72	74	66
Contact Lens History			
None	82 (53.9%)	73 (51.0%)	36 (55.4%)
Soft	69 (45.4%)	56 (39.2%)	21 (32.3%)
RGP	1 (0.7%)	13 (9.1%)	6 (9.2%)
PMMA	0	1 (0.7%)	2 (3.1)

F. DATA ANALYSIS AND RESULTS

1. Preoperative Characteristics

Tables 2, 3, and 4 contain the number of eyes enrolled stratified by the preoperative refraction. Note that per the protocol, the attempted correction corresponds with a subject's preoperative refractive error except for eyes undercorrected for monovision therapy. These eyes are excluded from the UCVA analysis, but are included in the remaining analyses.

TABLE 2 : Spherical Eyes
Stratified by Preop Sphere And Cylinder
Components of Cycloplegic Refraction

	CYLINDER				
SPHERE	0.0	-0.25	-0.5	-0.75	TOTAL
0.0 to 0.99	0	0	0	0	0
1.0 to 1.99	23 15.1%	9 5.9%	7 4.6%	1 0.7%	40 26.3%
2.0 to 2.99	22 14.5%	22 14.5%	18 11.8%	2 1.3%	64 42.1%
3.0 to 3.99	8 5.3%	6 3.9%	9 5.9%	0	23 15.1%
4.0 to 4.99	6 3.9%	2 1.3%	4 2.6%	0	12 7.9%
5.0 to 6.00	4 2.6%	1 0.7%	6 3.9%	2 1.3%	13 8.6%
TOTAL	63 41.4%	40 26.3%	44 28.9%	5 3.3%	152 100.0%

TABLE 3: Hyperopic Astigmatic Eyes
Stratified by Preop Sphere And Cylinder
Components of Cycloplegic Refraction

	CYLINDER						
SPHERE	0.0 to -0.9	-1.0 to -1.9	-2.0 to -2.9	-3.0 to -3.9	-4.0 to -4.9	-5.0 to -6.0	TOTAL
0.0 to 0.99	0	0	0	0	0	0	0
1.0 to 1.99	9 6.3%	7 4.9%	0	0	0	0	16 11.2%
2.0 to 2.99	16 11.2%	19 13.3%	3 2.1%	0	0	0	38 26.6%
3.0 to 3.99	12 8.4%	12 8.4%	8 5.6%	0	0	0	32 22.4%
4.0 to 4.99	2 1.4%	10 7.0%	3 2.1%	2 1.4%	2 1.4%	0	19 13.3%
5.0 to 6.00	6 4.2%	10 7.0%	7 4.9%	6 4.2%	2 1.4%	7 4.9%	38 26.6%
TOTAL	45 31.5%	58 40.6%	21 14.7%	8 5.6%	4 2.8%	7 4.9%	143 100.0%

TABLE 4: Mixed Astigmatic Eyes
Stratified by Preop Sphere And Cylinder
Components of Cycloplegic Refraction

	CYLINDER						
SPHERE	0.0 to -0.9	-1.0 to -1.9	-2.0 to -2.9	-3.0 to -3.9	-4.0 to -4.9	-5.0 to -6.0	TOTAL
0.0 to 0.99	0	10 15.4%	7 10.8%	2 3.1%	0	0	19 29.2%
1.0 to 1.99	0	5 7.7%	8 12.3%	5 7.7%	1 1.5%	2 3.1%	21 32.3%
2.0 to 2.99	0	0	1 1.5%	5 7.7%	1 1.5%	2 3.1%	9 13.8%
3.0 to 3.99	0	0	0	0	5 7.7%	5 7.7%	10 15.4%
4.0 to 4.99	0	0	0	0	2 3.1%	1 1.5%	3 4.6%
5.0 to 6.00	0	0	0	0	0	3 4.6%	3 4.6%
TOTAL	0	15 23.1%	16 24.6%	12 18.5%	9 13.8%	13 20.0%	65 100.0%

2. Postoperative results

a. Accountability

The percent of enrolled eyes accounted for at each visit was acceptable.

Table 5: Accountability of the Overall Cohort

		Day 1	1 Week	1 M	3 M	6 M	9 M
Enrolled: Primary	n	201	201	201	201	201	201
Fellow	n	159	159	159	159	159	159
TOTAL	n	360	360	360	360	360	360
Available for Analysis	**n**	**359**	**354**	**353**	**344**	**324**	**265**
Discontinued: Retreatment	n	0	0	0	0	20	66
Unrelated to treatment	n	0	0	0	0	0	1
Not Eligible for Interval	n	0	0	0	0	0	0
In Process*	n	0	0	0	0	0	0
Overdue/Missed Visit: Primary	n	0	2	3	9	9	17
Fellow	n	1	4	4	7	7	11
TOTAL	n	1	6	7	16	16	28
% Accountability [available/(available + Overdue)]		99.7%	98.3%	98.1%	95.6%	95.3%	90.4%

*In process refers to patients who were still eligible for the interval when the database was closed

Table 6: Available for Analysis Eyes at Each Follow-up					
	Preop	1 Month	3 Months	6 Months	9 Months
Spherical Hyperopic Eyes (total)	152	150	149	143	121
Monovision Eyes	27	26	26	22	18
Excluding Monovision Eyes	125	124	123	121	103
Hyperopic Astigmatic Eyes (total)	143	139	134	124	94
Monovision Eyes	15	15	14	14	11
Excluding Monovision Eyes	128	124	120	110	83
Mixed Astigmatic Eyes (total)	65	64	61	57	50
Monovision Eyes	3	3	3	3	3
Excluding Monovision Eyes	62	61	58	54	47

b. Stability of outcome

Tables 7 – 12 contain the stability analysis for the overall population, as well as for the 3 individual hyperopic cohorts. Note that for the mixed astigmatism cohort, stability analysis was performed with MR cylinder and not MRSE.

It was observed that except for the spherical cohort, each of the other groups experienced a change of MR not exceeding ± 1.0D in at least 95% of eyes over the 3-6 month window. Furthermore, the mean of the paired-differences of MR reached a change of less than |0.10| D during the same time window. The changes in the 6-9 months window for those cohorts remained at less than |0.10| D; thus, stability was demonstrated by 6 months postoperative.

The spherical cohort did not meet the same benchmarks as the other cohorts for the same time window of 3-6 months. However, given the small margins of differences and the outcomes of the 1-3 and 6-9 month time windows, it was determined that the 6 months stability time point would also apply to the spherical cohort.

TABLE 7: Stability of MRSE - Overall
(Eyes that had every exam through 9 Months)

Change in Spherical Equivalent Between		1 and 3 Months (n=245)	3 and 6 Months (n=245)	6 and 9 Months (n=245)
≤1.00	n %	241 98.4%	235 95.9%	239 97.6%
Mean Difference		+0.05	+0.10	+0.06
SD		0.41	0.43	0.46
95% CI		(0.00, 0.10)	(0.04, 0.15)	(0.00, 0.11)

TABLE 8: Stability of MRSE – Spherical Cohort
(Eyes that had every exam through 6 Months)

Change in Spherical Equivalent Between		1 and 3 Months (n=138)	3 and 6 Months (n=138)
≤1.00	n %	133 96.4%	130 94.2%
Mean Difference		+0.11	+0.12
SD		0.46	0.48
95% CI		(0.03, 0.19)	(0.04, 0.20)

TABLE 9: Stability of MRSE – Spherical Cohort
(Eyes that had every exam through 9 Months)

Change in Spherical Equivalent Between		1 and 3 Months (n=119)	3 and 6 Months (n=119)	6 and 9 Months (n=119)
≤1.00	n %	115 96.6%	112 94.1%	115 96.6%
Mean Difference		+0.08	+0.14	+0.03
SD		0.43	0.47	0.54
95% CI		(0.01, 0.16)	(0.06, 0.23)	(-0.07, 0.12)

TABLE 10: Stability of MRSE – Hyperopic Astigmatism Cohort
(Eyes that had every exam through 6 Months)

Change in Spherical Equivalent Between		1 and 3 Months (n=115)	3 and 6 Months (n=115)
≤1.00	n %	111 96.5%	112 97.4%
Mean Difference		+0.12	+0.07
SD		0.50	0.41
95% CI		(0.03, 0.21)	(-0.01, 0.14)

TABLE 11: Stability of MRSE – Hyperopic Astigmatism Cohort (Eyes that had every exam through 9 Months)				
Change in Spherical Equivalent Between		1 and 3 Months (n=85)	3 and 6 Months (n=85)	6 and 9 Months (n=85)
≤1.00	n %	85 100.0%	83 97.7%	83 97.7%
Mean Difference		+0.04	+0.04	+0.06
SD		0.41	0.44	0.39
95% CI		(-0.05, 0.13)	(-0.06, 0.13)	(-0.03, 0.14)

TABLE 12: Stability of manifest refraction cylinder– Mixed Astigmatism Cohort				
(Eyes that had every exam through 6 Months)				
Change in MR Cyl Between		1 and 3 Months (n=52)	3 and 6 Months (n=52)	
≤1.00	n %	52 100.0%	52 100.0%	
Mean Difference		-0.01	+0.03	
SD		0.39	0.34	
95% CI		(-0.12, 0.10)	(-0.06, 0.13)	
(Eyes that had every exam through 9 Months)				
Change in MR Cyl Between		1 and 3 Months (n=41)	3 and 6 Months (n=41)	6 and 9 Months (n=41)
≤1.00	n %	41 100.0%	41 100.0%	40 97.6
Mean Difference		-0.04	+0.07	-0.02
SD		0.35	0.32	0.37
95% CI		(-0.15, 0.07)	(-0.03, 0.17)	(-0.13, 0.10)

c. Effectiveness Outcomes

The key effectiveness outcomes of the spherical cohort at 6 and 9 months, stratified by diopters of preoperative cycloplegic refraction spherical equivalent, are presented in tables 13 - 14. A decrease in predictability and an increase in loss of 2 lines of BSCVA were noted for the 5.00 to 6.00 D range. As recommended by the Panel and concurred by FDA, this observation would not limit the approval range for this cohort, but would be a caution in the labeling.

TABLE 13: Spherical Cohort at Stability (6 months)
Key Efficacy Variables Stratified by Preop CRSE

Efficacy Variables	SE	0 to 0.99	1.0 to 1.99	2.0 to 2.99	3.0 to 3.99	4.0 to 4.99	5.0 to 6.00	Cum Total
BSCVA ≥ 20/20 Preop*		**n=1**	**n=41**	**n=44**	**n=15**	**n=10**	**n=4**	**n=115**
UCVA 20/20 or better if BSCVA 20/20 or better Preop*	n	1	26	21	5	4	0	57
	%	100.0%	63.4%	47.7%	33.3%	40.0%	0.0%	49.6%
		n=1	**n=42**	**n=44**	**n=15**	**n=10**	**n=9**	**n=121**
UCVA 20/20* or better	n	1	27	21	5	4	1	59
	%	100.0%	64.3%	47.7%	33.3%	40.0%	11.1%	48.8%
UCVA 20/25* or better	n	1	34	31	8	6	3	83
	%	100.0%	81.0%	70.5%	53.3%	60.0%	33.3%	68.6%
UCVA 20/40* or better	n	1	42	43	11	9	7	113
	%	100.0%	100.0%	97.7%	73.3%	90.0%	77.8%	93.4%
		n=1	**n=53**	**n=50**	**n=18**	**n=11**	**n=10**	**n=143**
MRSE ±0.50D of intended	n	1	38	38	7	6	3	93
	%	100.0%	71.7%	76.0%	38.9%	54.5%	30.0%	65.0%
MRSE ±1.00D of intended	n	1	50	47	13	9	5	125
	%	100.0%	94.3%	94.0%	72.2%	81.8%	50.0%	87.4%
MRSE ±2.00D of intended	n	1	52	50	18	11	9	141
	%	100.0%	98.1%	100.0%	100.0%	100.0%	90.0%	98.6%

* excluding monovision eyes

TABLE 14: Spherical Cohort at 9 months
Key Efficacy Variables Stratified by Preop CRSE

Efficacy Variables	SE	0 to 0.99	1.0 to 1.99	2.0 to 2.99	3.0 to 3.99	4.0 to 4.99	5.0 to 6.00	Cum Total
BSCVA ≥ 20/20 Preop*		**n=1**	**n=36**	**n=35**	**n=13**	**n=9**	**n=3**	**n=97**
UCVA 20/20 or better if BSCVA 20/20 or better Preop*		1 100.0%	22 61.1%	17 48.6%	5 38.5%	4 44.4%	0 0.0%	49 50.5%
		n=1	**n=37**	**n=35**	**n=13**	**n=9**	**n=8**	**n=103**
UCVA 20/20* or better	n %	1 100.0%	22 59.5%	17 48.6%	5 38.5%	4 44.4%	0 0.0%	49 47.6%
UCVA 20/25* or better	n %	1 100.0%	30 81.1%	25 71.4%	8 61.5%	6 66.7%	3 37.5%	73 70.9%
UCVA 20/40* or better	n %	1 100.0%	37 100.0%	34 97.1%	10 76.9%	9 100.0%	7 87.5%	98 95.1%
		n=1	**n=45**	**n=40**	**n=16**	**n=10**	**n=9**	**n=121**
MRSE ±0.50D of intended	n %	1 100.0%	35 77.8%	29/39 74.4%	6 37.5%	7 70.0%	3 33.3%	81/120 67.5%
MRSE ±1.00D of intended	n %	1 100.0%	43 95.6%	37/39 94.9%	13 81.3%	8 80.0%	4 44.4%	106/120 88.3%
MRSE ±2.00D of intended	n %	1 100.0%	45 100.0%	39/39 100.0%	15 93.8%	10 100.0%	9 100.0%	119/120 99.2%

*excluding monovision eyes

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Tables 15 and 16 display the key effectiveness outcomes of the hyperopic astigmatic cohort. At the 6 months stability time point, poor MRSE outcomes were noted for the group with preoperative MRSE of 4.00-4.99 D. Even though some of the outcomes for 5.0 – 5.99 D group improved, the N in that group was small. Thus, it cannot be concluded that the drop in outcomes for 4.0 –4.99 D group was an isolated event. It could very likely represent degradation of results with increase in pre-op MRSE. The outcomes at 9 months were consistently better across the entire dioptric range in comparison to the 6 month data, potentially because undercorrected eyes had exited the cohort for retreatments. A caution regarding the outcomes for hyperopic astigmatic eyes between 4.00 and 6.00 D MRSE is therefore included in the labeling.

TABLE 15: Hyperopic Astigmatic Cohort at Stability (6 months)
Key Efficacy Variables Stratified by Preop CRSE

Efficacy Variables	SE	0 to 0.99	1.0 to 1.99	2.0 to 2.99	3.0 to 3.99	4.0 to 4.99	5.0 to 6.00	Cum Total
BSCVA ≥ 20/20 PREOP*		**n=1**	**n=24**	**n=29**	**n=15**	**n=13**	**n=6**	**n=88**
UCVA 20/20 or better if BSCVA 20/20 or better Preop*	n	1	10	14	8	3	2	38
	%	100.0%	41.7%	48.3%	53.3%	23.1%	33.3%	43.2%
		n=1	**n=30**	**n=35**	**n=19**	**n=17**	**n=8**	**n=110**
UCVA 20/20* or better	n	1	11	15	9	3	2	41
	%	100.0%	36.7%	42.9%	47.4%	17.6%	25.0%	37.3%
UCVA 20/25* or better	n	1	19	26	12	5	3	66
	%	100.0%	63.3%	74.3%	63.2%	29.4%	37.5%	60.0%
UCVA 20/40* or better	n	1	29	33	16	14	7	100
	%	100.0%	96.7%	94.3%	84.2%	82.4%	87.5%	90.9%
		n=4	**n=34**	**n=38**	**n=22**	**n=18**	**n=8**	**n=124**
MRSE ±0.50D of intended	n	2	24	27	13	5	4	75
	%	50.0%	70.6%	71.1%	59.1%	27.8%	50.0%	60.5%
MRSE ±1.00D of intended	n	3	34	35	18	13	7	110
	%	75.0%	100.0%	92.1%	81.8%	72.2%	87.5%	88.7%
MRSE ±2.00D of intended	n	4	34	38	22	18	7	123
	%	100.0%	100.0%	100.0%	100.0%	100.0%	87.5%	99.2%

*excluding monovision eyes

TABLE 16: Hyperopic Astigmatic Cohort at 9 months
Key Efficacy Variables Stratified by Preop CRSE

Efficacy Variables	SE	0 to 0.99	1.0 to 1.99	2.0 to 2.99	3.0 to 3.99	4.0 to 4.99	5.0 to 6.00	Cum Total
BSCVA ≥ 20/20 PREOP*		**n=1**	**n=18**	**n=24**	**n=11**	**n=7**	**n=5**	**n=66**
UCVA 20/20 or better if BSCVA 20/20 or better Preop*	n %	1 100.0%	13 72.2%	12 50.0%	7 63.6%	3 42.9%	2 40.0%	38 57.6%
		n=1	**n=22**	**n=30**	**n=14**	**n=8**	**n=8**	**n=83**
UCVA 20/20* or better	n %	1 100.0%	13 59.1%	16 53.3%	8 57.1%	3 37.5%	2 25.0%	43 51.8%
UCVA 20/25* or better	n %	1 100.0%	18 81.8%	22 73.3%	10 71.4%	4 50.0%	4 50.0%	59 71.1%
UCVA 20/40* or better	n %	1 100.0%	22 100.0%	29 96.7%	13 92.9%	7 87.5%	7 87.5%	79 95.2%
		n=3	**n=26**	**n=32**	**n=16**	**n=9**	**n=8**	**n=94**
MRSE ±0.50D of intended	n %	2 66.7%	19 73.1%	23 71.9%	12 75.0%	5 55.6%	5 62.5%	66 70.2%
MRSE ±1.00D of intended	n %	2 66.7%	24 92.3%	31 96.9%	15 93.8%	7 77.8%	7 87.5%	86 91.5%
MRSE ±2.00D of intended	n %	3 100.0%	26 100.0%	31 96.9%	16 100.0%	9 100.0%	8 100.0%	93 98.9%

*excluding monovision eyes

The analyses of the cylindrical component of the hyperopic astigmatic eyes are presented in Tables 17 (scalar) and 18 (vector). The sponsor utilized the Alpins method for calculating vectoral change. This method was described in Alpins, N., "A new method of analyzing vectors for changes in astigmatism", *Journal of Cataract and Refractive Surgery*, Vol 19, July 1993.

The results of the cylindrical component of the hyperopic astigmatic eyes did not raise any concern that would limit the cylinder treatment range or would need to be conveyed in the labeling. It was noted, however, that at 1, 3, and 6 months, small astigmatic errors were consistently overcorrected and large errors were consistently undercorrected (% Achieved results). Although these deviations from intended correction were not serious, they appeared to be inherent to this device.

TABLE 17: Hyperopic Astigmatic Cohort
Accuracy of manifest cylinder

CYLINDER	1 Month (n=138)	3 Months (n=133)	6 Months (n=124)	9 Months (n=94)
Mean ± SD	-0.61 ± 0.59	-0.72 ± 0.65	-0.64 ± 0.64	-0.50 ± 0.53
Attempted	-1.64 ± 1.26	-1.61 ± 1.19	-1.57 ± 1.18	-1.37 ± 0.98
Achieved	-1.11 ± 1.10	-1.03 ± 0.93	-1.02 ± 0.92	-0.95 ± 0.88
% Achieved	63 ± 35	63 ± 35	65 ± 33	67 ± 36
≤0.50D	84 60.9%	71 53.4%	74 60.0%	59 62.8%
≤1.00D	117 84.8%	105 79.0%	103 83.1%	86 91.5%

Tables 19 and 20 contain the key safety variables for the mixed astigmatic cohort, stratified by the preoperative absolute amount of power difference between the two meridians. It is noted that the predictability of the 3.00 to 3.99 D group in this cohort was poor at 6 months, but improved by 9 months. The decrease in predictability of the 3.0 –3.99 D did not appear to represent a pattern of worsening outcomes with increase in pre-op MRSE since the 4.00 -6.00 D group's outcomes were acceptable. Furthermore, UCVA outcomes for 3.00 –3.99 D group were acceptable.

The analyses of the cylindrical component of the mixed astigmatic eyes are presented in Table 21. The same Alpins method for calculating vectoral changes was used. The cylinder outcomes for this cohort were acceptable. Unlike the hyperopic astigmatic cohort, no particular trend is noted in the cylinder correction of the mixed astigmatic cohort.

TABLE 18: Hyperopic Astigmatism Cohort
Vector analysis of astigmatism

Baseline Cylinder	n	Intended Vector (A)	Achieved Vector (B)	Difference Vector (C)	% Achieved (B/A)	Angle of error (a)	Index of Success (C/A)
3 MONTHS							
ALL	133	1.62 ± 1.20 (1.41, 1.82)	1.62 ± 0.91 (1.46, 1.77)	0.72 ± 0.65 (0.62, 0.84)	118 ± 55 (108, 127)	10.5 ± 15 (7.9, 13.0)	0.59 ± 0.59 (0.49, 0.69)
0.0 to 0.9	39	0.66 ± 0.12 (0.62, 0.70)	0.94 ± 0.42 (0.81, 1.08)	0.56 ± 0.45 (0.42, 0.71)	148 ± 72 (125, 171)	15.7 ± 17.9 (9.9, 21.5)	0.92 ± 0.81 (0.66, 1.18)
1.0 to 1.9	56	1.23 ± 0.27 (1.16, 1.30)	1.47 ± 0.53 (1.33, 1.61)	0.62 ± 0.51 (0.48, 0.75)	122 ± 43 (110, 133)	9.3 ± 14.9 (5.3, 13.3)	0.54 ± 0.48 (0.41, 0.67)
2.0 to 2.9	21	2.34 ± 0.28 NA**	2.04 ± 0.62 NA**	0.68 ± 0.62 NA**	87 ± 24 NA**	6.9 ± 12.1 NA**	0.29 ± 0.26 NA**
3.0 to 3.9	8	3.22 ± 0.25 NA**	2.42 ± 0.83 NA**	1.31 ± 0.72 NA**	76 ± 28 NA**	7.1 ± 8.1 NA**	0.41 ± 0.23 NA**
4.0 to 4.9	3	4.25 ± 0.0 NA**	3.48 ± 0.59 NA**	1.25 ± 0.75 NA**	82 ± 14 NA**	7.5 ± 4.6 NA**	0.29 ± 0.18 NA**
5.0 to 6.0	6	5.38 ± 0.38 NA**	3.84 ± 1.10 NA**	1.96 ± 1.19 NA**	72 ± 21 NA**	6.1 ± 6.1 NA**	0.36 ± 0.21 NA**
6 MONTHS							
ALL	124	1.57 ± 1.18 (1.36, 1.78)	1.48 ± 0.87 (1.33, 1.64)	0.64 ± 0.64 (0.53, 0.76)	109 ± 50 (100, 118)	8.8 ± 12.5 (6.6, 11.0)	0.49 ± 0.52 (0.40, 0.58)
0.0 to 0.9	39	0.67 ± 0.12 (0.63, 0.71)	0.84 ± 0.40 (0.71, 0.97)	0.42 ± 0.44 (0.27, 0.56)	130 ± 67 (108, 152)	11.2 ± 16.4 (5.9, 16.5)	0.66 ± 0.75 (0.42, 0.90)
1.0 to 1.9	52	1.25 ± 0.27 (1.17, 1.32)	1.39 ± 0.54 (1.24, 1.54)	0.56 ± 0.46 (0.43, 0.69)	112 ± 38 (101, 122)	8.7 ± 11.1 (5.6, 11.8)	0.47 ± 0.40 (0.36, 0.58)
2.0 to 2.9	19	2.34 ± 0.27 NA**	1.95 ± 0.54 NA**	0.75 ± 0.63 NA**	84 ± 22 NA**	8.0 ± 10.2 NA**	0.32 ± 0.26 NA**
3.0 to 3.9	6	3.17 ± 0.26 NA**	2.25 ± 0.79 NA**	1.13 ± 0.61 NA**	71 ± 26 NA**	3.5 ± 3.7 NA**	0.36 ± 0.20 NA**
4.0 to 4.9	3	4.17 ± 0.14 NA**	3.50 ± 0.34 NA**	0.92 ± 0.72 NA**	84 ± 10 NA**	4.5 ± 5.5 NA**	0.22 ± 0.17 NA**
5.0 to 6.0	5	5.55 ± 0.45 NA**	3.53 ± 1.20 NA**	2.10 ± 1.38 NA**	64 ± 23 NA**	2.7 ± 3.2 NA**	0.37 ± 0.23 NA**
9 MONTHS							
ALL	94	1.37 ± 0.98 (1.17, 1.57)	1.37 ± 0.82 (1.20, 1.54)	0.50 ± 0.53 (0.39, 0.61)	110 ± 45 (101, 199)	9.8 ± 15.7 (6.6, 13.0)	0.46 ± 0.53 (0.35, 0.57)
0.0 to 0.9	35	0.67 ± 0.12 (0.63, 0.72)	0.82 ± 0.35 (0.70, 0.94)	0.36 ± 0.39 (0.22, 0.49)	124 ± 55 (105, 143)	12.6 ± 20.7 (5.5, 19.8)	0.58 ± 0.67 (0.35, 0.81)
1.0 to 1.9	41	1.22 ± 0.27 (1.13, 1.30)	1.31 ± 0.47 (1.16, 1.46)	0.54 ± 0.53 (0.37, 0.70)	109 ± 39 (97, 121)	10.3 ± 13.1 (6.1, 14.4)	0.47 ± 0.48 (0.32, 0.62)
2.0 to 2.9	11	2.43 ± 0.28 NA**	2.28 ± 0.49 NA**	0.50 ± 0.40 NA**	93 ± 17 NA**	4.2 ± 5.1 NA**	0.21 ± 0.17 NA**
3.0 to 3.9	3	3.17 ± 0.29 NA**	2.31 ± 1.25 NA**	0.92 ± 1.01 NA**	72 ± 34 NA**	1.7 ± 3.0 NA**	0.31 ± 0.34 NA**
4.0 to 4.9	2	4.25 ± 0.0 NA**	4.05 ± 0.29 NA**	0.25 ± 0.35 NA**	95 ± 7 NA**	1.0 ± 1.5 NA**	0.06 ± 0.08 NA**
5.0 to 6.0	2	5.13 ± 0.18 NA**	3.16 ± 0.13 NA**	2.00 ± 0.0 NA**	62 ± 1 NA**	2.6 ± 1.9 NA**	0.39 ± 0.01 NA**

*Mean ± SD shown with the 95% confidence interval in brackets ** CI not applicable (n<25)
***No eyes available

TABLE 19: Mixed Astigmatic Cohort at stability (6 Months)
Key Efficacy Variables Stratified By The Preoperative Absolute Amount Of Power Difference Between The Two Meridians.

Efficacy Variables	SE	1.0 to 1.99	2.0 to 2.99	3.0 to 3.99	4.0 to 4.99	5.00 to 6.00	Cum Total
BSCVA ≥ 20/20 PREOP*		**n=13**	**n=13**	**n=7**	**n=4**	**n=3**	**n=40**
UCVA 20/20 or better if BSCVA 20/20 or better Preop*	N	7	6	3	1	1	18
	%	53.8%	46.2%	42.9%	25.0%	33.3%	45.0%
		n=13	**n=15**	**n=9**	**n=8**	**n=9**	**n=54**
UCVA 20/20* or better	N	7	7	4	3	4	25
	%	53.8%	46.7%	44.4%	37.5%	44.4%	46.3%
UCVA 20/25* or better	N	9	10	8	7	6	40
	%	69.2%	66.7%	88.9%	87.5%	66.7%	74.1%
UCVA 20/40* or better	N	12	14	8	8	8	50
	%	92.3%	93.3%	88.9%	100.0%	88.9%	92.6%
		n=13	**n=15**	**n=11**	**n=8**	**n=10**	**n=57**
MRSE ±0.50D of intended	N	10	10	4	5	8	37
	%	76.9%	66.7%	36.4%	62.5%	80.0%	64.9%
MRSE ±1.00D of intended	N	10	15	8	8	9	50
	%	76.9%	100.0%	72.7%	100.0%	90.0%	87.7%
MRSE ±2.00D of intended	N	13	15	11	8	10	57
	%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

*excluding monovision eyes

TABLE 20: Mixed Astigmatic Cohort at 9 Months
Key Efficacy Variables Stratified By The Preoperative Absolute Amount Of Power Difference Between The Two Meridians.

Efficacy Variables	SE	1.0 to 1.99	2.0 to 2.99	3.0 to 3.99	4.0 to 4.99	5.00 to 6.00	Cum Total
BSCVA ≥ 20/20 PREOP*		n=15	n=12	n=5	n=3	n=2	n=37
UCVA 20/20 or better if BSCVA 20/20 or better Preop*	N	8	6	3	1	1	19
	%	53.3%	50.0%	60.0%	33.3%	50.0%	51.4%
		n=15	n=12	n=8	n=6	n=6	n=47
UCVA 20/20* or better	N	8	6	4	1	3	22
	%	53.3%	50.0%	50.0%	16.7%	50.0%	46.8%
UCVA 20/25* or better	N	11	9	5	4	4	33
	%	73.3%	75.0%	62.5%	66.7%	66.7%	70.2%
UCVA 20/40* or better	N	13	12	7	6	6	44
	%	86.7%	100.0%	87.5%	100.0%	100.0%	93.6%
		n=15	n=12	n=10	n=6	n=7	n=50
MRSE ±0.50D of intended	N	12	9	9	5	6	41
	%	80.0%	75.0%	90.0%	83.3%	85.7%	82.0%
MRSE ±1.00D of intended	N	14	11	10	6	7	48
	%	93.3%	91.7%	100.0%	100.0%	100.0%	96.0%
MRSE ±2.00D of intended	N	15	12	10	6	7	50
	%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

*excluding monovision eyes

TABLE 21: Mixed Astigmatic Cohort
Vector Analysis Of Astigmatism

Baseline Cylinder	n	Intended Vector (A)	Achieved Vector (B)	Difference Vector (C)	% Achieved (B/A)	Angle of error (a)	Index of Success (C/A)
6 MONTHS							
ALL	57	3.21 ± 1.46 (2.82, 3.59)	2.85 ± 1.29 (2.51, 3.20)	0.55 ± 0.49 (0.42, 0.68)	90 ± 14 (86, 94)	3.1 ± 3.6 (2.1, 4.0)	0.17 ± 0.15 (0.13, 0.21)
1.0 to 1.9	13	1.58 ± 0.19 NA**	1.47 ± 0.31 NA**	0.25 ± 0.27 NA**	93 ± 14 NA**	3.9 ± 5.3 NA**	0.16 ± 0.18 NA**
2.0 to 2.9	15	2.33 ± 0.29 NA**	2.15 ± 0.45 NA**	0.30 ± 0.34 NA**	92 ± 16 NA**	1.8 ± 2.2 NA**	0.13 ± 0.15 NA**
3.0 to 3.9	11	3.23 ± 0.31 NA**	3.03 ± 0.47 NA**	0.66 ± 0.47 NA**	94 ± 16 NA**	4.0 ± 3.6 NA**	0.21 ± 0.15 NA**
4.0 to 4.9	8	4.53 ± 0.28 NA**	3.57 ± 0.42 NA**	1.16 ± 0.40 NA**	79 ± 7 NA**	4.1 ± 3.7 NA**	0.26 ± 0.10 NA**
5.0 to 6.0	10	5.55 ± 0.35 NA**	4.95 ± 0.72 NA**	0.70 ± 0.52 NA**	89 ± 9 NA**	2.0 ± 1.9 NA**	0.13 ± 0.10 NA**
9 MONTHS							
ALL	50	3.01 ± 1.48 (2.59, 3.43)	2.76 ± 1.41 (2.36, 3.16)	0.45 ± 0.44 (0.32, 0.58)	92 ± 17 (87, 97)	3.1 ± 4.8 (1.8, 4.5)	0.17 ± 0.19 (0.11, 0.22)
1.0 to 1.9	15	1.55 ± 0.19 NA**	1.41 ± 0.42 NA**	0.35 ± 0.42 NA**	91 ± 25 NA**	5.2 ± 7.1 NA**	0.23 ± 0.28 NA**
2.0 to 2.9	12	2.29 ± 0.26 NA**	2.23 ± 0.36 NA**	0.27 ± 0.33 NA**	97 ± 10 NA**	2.4 ± 3.7 NA**	0.12 ± 0.14 NA**
3.0 to 3.9	10	3.25 ± 0.33 NA**	2.93 ± 0.49 NA**	0.60 ± 0.46 NA**	91 ± 15 NA**	3.1 ± 3.4 NA**	0.19 ± 0.14 NA**
4.0 to 4.9	6	4.54 ± 0.29 NA**	3.70 ± 0.44 NA**	0.96 ± 0.29 NA**	81 ± 6 NA**	2.4 ± 2.3 NA**	0.21 ± 0.07 NA**
5.0 to 6.0	7	5.71 ± 0.27 NA**	5.49 ± 0.50 NA**	0.32 ± 0.43 NA**	96 ± 7 NA**	0.7 ± 1.2 NA**	0.06 ± 0.08 NA**

*Mean ± SD shown with the 95% confidence interval in brackets ** CI not applicable (n<25)
***No eyes available

d. Safety Outcomes

The analysis of safety was based on the entire cohort and by each indication. The key safety outcomes for this study are presented in Tables 22 and 23. The loss of BSCVA noted for the higher hyperopes, shown in Table 23, will be noted in the labeling. The adverse reactions noted at each exam are reported in Table 24. Given the low rates of adverse reactions, their stratification by indication is not included in this summary. The benchmark for each adverse event is a rate of less than 1 % per event. Overall, the device was deemed reasonably safe.

TABLE 22: Summary of Key Safety Variables by Visit

Safety Variables	1 Month			3 Months			6 Months			9 Months		
	Sph Hyp	Hyp Astig	Mixed Astig	Sph Hyp	Hyp Astig	Mixed Astig	Sph Hyp	Hyp Astig	Mixed Astig	Sph Hyp	Hyp Astig	Mixed Astig
Loss of >2 Lines BSCVA	3/149 2.0%	3/135 2.2%	1/58 1.7%	0/149	0/127	0/56	0/141	0/121	0/52	0/118	0/90	0/46
Loss of 2 Lines BSCVA	14/149 9.4%	16/135 11.9%	1/58 1.7%	8/149 5.4%	7/127 5.5%	2/56 3.6%	5/141 3.5%	7/121 5.8%	1/52 1.9%	4/118 3.4%	4/90 4.4%	1/46 2.2%
BSCVA worse than 20/40	0/149	1/138 0.7%	0/62	0/149	0/130	0/60	0/141	0/124	0/56	0/118	0/93	0/50
Increase >2D Cylinder	1/149 0.7%	0/138	0/64	0/149	0/133	0/61	0/143	0/124	0/57	0/120	0/94	0/50
BSCVA worse than 20/25 if 20/20 or better preop.	10/138 7.2%	8/114 7.0%	1/48 2.1%	5/138 3.6%	2/107 1.9%	1/45 2.2%	2/132 1.5%	3/101 3.0%	0/41	2/109 1.8%	0/75	0/39

TABLE 23: Loss Of ≥ 2 Lines BSCVA Stratified By Indication And Diopter						
	6 MONTHS			9 MONTHS		
Spherical Equivalent						
	Spherical Hyperopia	Hyperopic Astigm	Mixed Astigm	Spherical Hyperopia	Hyperopic Astigm	Mixed Astigm
-1.01 to -2	--	--	0/2 0.0%	--	--	0/2 0.0%
-0.01 to –1.00	--	--	0/18 0.0%	--	--	1/17 5.9%
0.0- 0.9	0/1 0.0%	0/4 0.0%	0/22 0.0%	0/1 0.0%	0/3 0.0%	0/22 0.0%
1.0- 1.9	3/53 5.7%	3/34 8.8%	1/8 12.5%	2/45 4.4%	2/26 7.7%	0/5 0.0%
2.0- 2.9	1/49 2.0%	0/36 0.0%	0/2 0.0%	2/38 5.3%	2/30 6.7%	0/0 --
3.0-3.9	0/17 0.0%	0/22 0.0%	--	0/15 0.0%	0/15 0.0%	--
4.0- 4.9	0/11 0.0%	3/18 16.7%	--	0/10 0.0%	0/9 0.0%	--
5.0- 6.0	1/10 10.0%	1/7 14.3%	--	0/9 0.0%	0/7 0.0%	--

Table 24: Adverse Reactions for the Combined Cohort by Visit								
	1 Month		3 Months		6 Months		9 Months	
	n/N	%	n/N	%	n/N	%	n/N	%
ADVERSE EVENTS								
Rolled flap edge with trace corneal melt	0/353	**0.0**	0/344	**0.0**	1/324	**0.3**	0/265	**0.0**
COMPLICATIONS								
Corneal abrasion	0/353	**0.0**	0/344	**0.0**	1/324	**0.3**	0/265	**0.0**
Corneal folds/Striae/Wrinkles	3/353	**0.8**	0/344	**0.0**	0/324	**0.0**	1/265	**0.4**
Corneal opacities	3/353	**0.8**	6/344	**1.7**	1/324	**0.3**	2/265	**0.8**
Double/ghost images	2/353	**0.6**	2/344	**0.6**	5/324	**1.5**	2/265	**0.8**
Epithelium in the interface	6/353	**1.7**	7/344	**2.0**	5/324	**1.5**	3/265	**1.1**
Feeling of something in the eye	2/353	**0.6**	2/344	**0.6**	1/324	**0.3**	0/265	**0.0**
Interface debris	10/353	**2.8**	7/344	**2.0**	5/324	**1.5**	1/265	**0.4**
Irregular epithelium	1/353	**0.3**	0/344	**0.0**	0/324	**0.0**	0/265	**0.0**
Iron line or ring	0/353	**0.0**	0/344	**0.0**	1/324	**0.3**	2/265	**0.8**
Isolated cells in interface	0/353	**0.0**	1/344	**0.3**	2/324	**0.6**	1/265	**0.4**
Lagophthalmos	1/353	**0.3**	0/344	**0.0**	0/324	**0.0**	0/265	**0.0**
Pain	1/353	**0.3**	0/344	**0.0**	0/324	**0.0**	0/265	**0.0**
Sterile Interface Inflammation	1/353	**0.3**	0/344	**0.0**	0/324	**0.0**	0/265	**0.0**
Superficial punctate keratitis (SPK)	20/353	**5.7**	17/344	**4.9**	10/324	**3.1**	14/265	**5.3**

The following other complications occurred at unscheduled visits at 1 month or later: conjunctival injection (1), corneal folds/striae/wrinkles (4), corneal opacities (2), interface debris (8), iron line/ring (3), subconjunctival hemorrhage (1), superficial punctate keratitis (14), trichiasis (1), and vacuoles (1).

Each of the following ocular findings was reported at 6 months (n=265) at a rate of 0.6% or less: allergic conjunctivitis, vitreous floater, cotton wool spot, and drusen.

Lens findings (cataracts) were reported postoperatively in 14 eyes of 8 patients. All of these patients experienced lens changes due to age (range 59 to 73 years old). These findings included nuclear sclerosis, cortical spoking, and posterior subcapsular cataract. No eyes had a loss of more than 2 lines of best spectacle corrected visual acuity (with glasses). Only one eye had a related loss of 2 lines of best spectacle corrected visual acuity. All eyes had a last-reported best-corrected visual acuity of 20/32 or better.

The events reported on the patient questionnaire at the 6-month visit are listed in Table 25.

A subgroup study on contrast sensitivity testing was performed at 2 sites. Preoperative and 6-month postoperative data from 95 spherical, 50 hyperopic astigmatic, and 23 mixed astigmatic eyes were analyzed. However, results were unreliable and no conclusions could be made.

A subgroup study on central endothelial cell density was performed at 2 sites. Endothelial cell density was determined pre-operatively, and at 3 and 6 months postoperatively. Data were available for 144 eyes at 3 months and 132 eyes at 6 months. In general, an increase in cells from preoperative was observed, with the largest increase being 4.2% in contact lens wearers at 6 months (n=71). A clinically significant change in endothelial cell density was considered to be $\geq$ 10% due to the inherent error in the measurements. There was no significant change in endothelial cell density at any time point from preoperative density for the subgroup of eyes studied.

Table 25: Subjective Symptoms at 6 Months

Subjective Responses	Hyperopia without astigmatism				Hyperopic Astigmatism				Mixed Astigmatism			
		Unchanged or Better*	Worse	Sig. Worse		Unchanged or Better*	Worse	Sig. Worse		Unchanged or Better*	Worse	Sig. Worse
	N	%	%	%	*N*	%	%	%	*N*	%	%	%
Blurring of vision	*132*	88.6	9.8	1.5	*111*	82.9	15.3	1.8	*53*	88.7	7.5	3.8
Burning	*133*	97.0	2.3	0.8	*113*	90.3	8.0	1.8	*53*	92.5	7.5	0.0
Double vision	*132*	90.2	8.3	1.5	*111*	90.1	6.3	3.6	*53*	98.1	1.9	0.0
Dryness	*132*	80.3	16.7	3.0	*113*	77.0	17.7	5.3	*53*	73.6	24.5	1.9
Excessive tearing	*132*	98.5	1.5	0.0	*111*	98.2	1.8	0.0	*52*	100	0.0	0.0
Feeling of something in eye	*133*	93.2	5.3	1.5	*113*	92.0	5.3	2.7	*53*	94.3	5.7	0.0
Fluctuation of vision	*133*	78.2	15.8	6.0	*111*	77.5	20.7	1.8	*53*	88.7	11.3	0.0
Glare	*133*	77.5	21.8	0.8	*113*	79.6	18.6	1.8	*53*	77.4	22.6	0.0
Halos	*132*	84.8	12.9	2.3	*111*	74.8	20.7	4.5	*53*	73.6	26.4	0.0
Headache	*132*	97.0	3.0	0.0	*110*	95.5	2.7	1.8	*53*	96.2	3.8	0.0
Light sensitivity	*133*	72.2	26.3	1.5	*112*	76.8	21.4	1.8	*53*	79.2	20.8	0.0
Night driving difficulty	*133*	88.7	9.0	2.3	*113*	84.1	14.2	1.8	*53*	79.2	13.2	7.5
Pain	*132*	96.2	3.0	0.8	*110*	94.5	4.5	0.9	*53*	96.2	3.8	0.0
Quality of vision	*132*	95.5	4.5	0.0	*115*	94.8	5.2	0.0	*53*	94.3	1.9	3.8
Redness	*133*	88.0	11.3	0.8	*112*	92.0	5.4	2.7	*53*	96.2	3.8	0.0

* Unchanged or better includes responses rated as unchanged, better, or significantly better than before surgery

e. Retreatments

Retreatment was performed in 18 (11.8%) spherical hyperopic eyes, 40 (28.0%) hyperopic astigmatic eyes, and 17 (26.1%) mixed astigmatic eyes. Seven eyes were retreated for overcorrection of sphere and/or cylinder, all of which had low (≤+2.50D) hyperopic sphere, including 5 mixed astigmatic eyes with less than 1D of sphere. Eleven eyes were retreated for induced cylinder with or without sphere undercorrection. The remaining 57 eyes were retreated for undercorrection of sphere and/or cylinder from the monovision or emmetropia target. Six were retreated with another laser and exited this study. The remaining 69 eyes were retreated with the study laser. In addition, one eye received two retreatments for a cycloplegic refraction of +6.00/-5.50 x 5 (prior to any treatment).

Approximately one-half of all retreated eyes had a preoperative cycloplegic sphere of +4D to +6D (prior to any treatment). Of the 57 eyes treated for hyperopic or mixed astigmatism, 24.6% had a preoperative cylinder of -4 to –6D. This tendency for the eyes in the higher dioptric level to receive retreatments is noted in the labeling.

The key safety and effectiveness variables for the retreated eyes are provided in Table 26. In addition, these adverse events and complications occurred at 1 to 6 months after retreatment: epithelium in the interface (3 eyes) and double/ghost images (4 eyes). Although the retreatment outcomes did not raise any concern, they were insufficient to support a retreatment claim for the device.

The events reported on the patient questionnaire at 6 months post-retreatment are listed in Table 27.

TABLE 26: Retreated Eyes
Summary Of Key Safety And Efficacy Variables by Visits Made After Retreatments

Efficacy Variables		**1 Month**	**3 Months**	**6 Months**	**9 Months**
BSCVA ≥ 20/20 Preop*		**n=42**	**n=38**	**n=17**	**n=4**
UCVA 20/20 or better if BSCVA 20/20 or better Preop*	N %	21 50.0%	20 52.6%	5 29.4%	4 100.0%
		n=57	**n=50**	**n=23**	**n=7**
UCVA 20/20 or better *	N %	22 38.6%	22 44.0%	5 21.7%	4 57.1%
UCVA 20/25 or better*	N %	36 63.2%	39 78.0%	14 60.9%	5 71.4%
UCVA 20/40 or better *	N %	51 89.5%	48 96.0%	22 95.7%	7 100.0%
		n=67	**n=58**	**n=28**	**n=7**
MRSE ±0.50D of intended	N %	44/66 66.7%	45/57 78.9%	19 67.9%	4 57.1%
MRSE ±1.00D of intended	N %	63/66 95.5%	54/57 94.7%	27 96.4%	7 100.0%
MRSE ±2.00D of intended	N %	66/66 100.0%	57/57 100.0%	28 100.0%	7 100.0%
Safety Variables		**n=67**	**n=58**	**n=28**	**n=7**
Loss of >2 Lines BSCVA†	N %	2/66 3.0%	1/54 1.9%	0/27 0.0%	0 0.0%
Loss of 2 Lines BSCVA†	N %	5/66 7.6%	7/54 13.0%	1/27 3.7%	1/7 14.3%
BSCVA worse than 20/40	N %	0/66 0.0%	1/54 1.9%	0/27 0.0%	0 0.0%
Increase >2D Cylinder	N %	0/66 0.0%	0/57 0.0%	0/28 0.0%	0 0.0%
BSCVA ≥ 20/20 Preop		**n=49**	**n=44**	**n=19**	**n=4**
BSCVA worse than 20/25 if 20/20 or better preoperatively	N %	3/49 6.1%	5/41 12.2%	0/19 0.0%	0 0.0%

*Not including monovision eyes
† BSCVA post-retreatment compared to BSCVA prior to any laser treatment

TABLE 27: Retreated Eyes
Change In Symptoms At 6 Months Post-Retreatment as Compared to Pre-Retreatment

n %	Sig. Better	Better	No Change	Worse	Sig.Worse	Not Reported	Total
Light Sensitivity	1 4.3%	2 8.7%	12 52.2%	8 34.8%	0 0.0%	5	28
Headache	2 8.3%	3 12.5%	18 75.0%	1 4.2%	0 0.0%	4	28
Pain	3 13.0%	1 4.3%	19 82.6%	0 0.0%	0 0.0%	5	28
Redness	2 8.7%	1 4.3%	18 78.3%	2 8.7%	0 0.0%	5	28
Excessive Tearing	2 8.7%	3 13.0%	18 78.3%	0 0.0%	0 0.0%	5	28
Burning	2 8.7%	3 13.0%	14 60.9%	4 17.4%	0 0.0%	5	28
Gritty Feeling	2 8.7%	3 13.0%	17 73.9%	1 4.3%	0 0.0%	5	28
Glare	1 4.2%	3 12.5%	12 50.0%	7 29.2%	1 4.2%	4	28
Halos	1 4.2%	2 8.3%	14 58.3%	7 29.2%	0 0.0%	4	28
Dryness	1 4.2%	3 12.5%	12 50.0%	8 33.3%	0 0.0%	4	28
Night Driving Difficulty	3 12.5%	4 16.7%	12 50.0%	5 20.8%	0 0.0%	4	28
Blurring of Vision	4 17.4%	4 17.4%	10 43.5%	5 21.7%	0 0.0%	5	28
Double Vision	1 4.2%	1 4.2%	17 70.8%	5 20.8%	0 0.0%	4	28
Fluctuation of Vision	0 0.0%	2 8.3%	11 45.8%	10 41.7%	1 4.2%	4	28

f. Factors associated with outcomes

These factors were noted in the study and are included as precautions in the labeling:

- Eye with greater than 5.0D of hyperopia may have lower predictability of refractive outcome and improvement in uncorrected visual acuity (vision without glasses or contact lenses) than eyes with lower levels of hyperopia.

- Hyperopic astigmatism eyes with greater than 4.0D MRSE before surgery may have lower predictability of refractive outcome and improvement in uncorrected visual acuity (vision without glasses or contact lenses) than eyes with lower levels of MRSE. MRSE is the amount of hyperopic astigmatism calculated based on the glasses prescription. These eyes may be more likely to experience a reduction of two lines in their best corrected visual acuity (vision with glasses or contact lenses) and to require additional treatment (retreatment).

- Older patients and women on hormone replacement therapy may be less likely to achieve uncorrected visual acuity (vision without glasses or contact lenses) of 20/20 or better.

g. Patient Satisfaction

Reported in Table 28 are the assessments made at the 6 month visit.

Table 28: Patient Satisfaction Results At 6 Months

	Hyperopia without astigmatism		**Hyperopic Astigmatism**		**Mixed Astigmatism**	
	N	%	*n/N*	%	*n/N*	%
Extremely Satisfied	*53/133*	39.8	*31/112*	27.7	*21/53*	39.6
Satisfied	*48/133*	36.1	*45/112*	40.2	*20/53*	37.7
Not Sure	*16/133*	12.0	*22/112*	19.6	*6/53*	11.3
Unsatisfied	*16/133*	12.0	*11/112*	9.8	*5/53*	9.4
Extremely Unsatisfied	*0/133*	0.0	*3/112*	2.7	*1/53*	1.9

h. Device failures

Seventeen eyes experienced interruptions during the surgical procedure due to laser system failures: a defective programmable computer chip (1) and timing error (16). All eyes achieved UCVA of 20/40 or better at the last reported visit. Except two, the other 15 eyes had a BSCVA of 20/25 and were within 1 line of preoperative. The two eyes were 20/32 and within 2 lines of preoperative BSCVA, with one eye having a BSCVA of 20/20 at the previous one month visit.

During the treatment of two eyes, the laser repetition rate was below specification, firing at 9 to 11 Hz. The cause was a failure of the service engineer to reset calibration prior to exiting service mode. Both eyes had a UCVA of 20/40 or better, and no loss of BSCVA at the last reported visit.

All incidents were investigated and the causes fixed to prevent a reoccurrence.

XI. CONCLUSIONS DRAWN FROM THE CLINICAL STUDY

The data in this application support reasonable assurance of safety and effectiveness of the LADARVision® Excimer Laser System when used in accordance with the indications for use.

XII. PANEL RECOMMENDATION

At an advisory meeting held on March 17, 2000, the Ophthalmic Devices Panel recommended that the Summit Autonomous PMA for the LADARVision® Excimer Laser System be conditionally approved, on the conditions that:

1. These labeling changes be made:

   - Include patient symptoms categories of worse and significantly worse;
   - Include unsatisfied and very unsatisfied data in reader friendly language;
   - Include quality of vision categories of worse and significantly worse;
   - Include dryness rates;
   - Change Patient Information on p. 18 regarding loss of BSCVA;
   - Include cylinder > 1 D in the reporting of cylinder induction;
   - Highlight the declining predictability in eyes with greater than 4 D MRSE;
   - Highlight the declining UCVA in eyes with greater than 4 D MRSE;
   - Note that insufficient data are available for the assessment of safety and effectiveness of retreatments;
   - Discuss age and hormonal replacement therapy;
   - Discuss the unknown effects of race, since study population was primarily Caucasians;
   - Include BSCVA loss of greater than or equal to 2 lines;
   - Add that risks of refractive instability increase in patients w/ 2 or more lines loss of BSCVA;
   - Note that treatment zone is 9.0 mm; thus, flap size should allow for it; and,
   - Include patient outcomes within the first week and month of treatment in both patient and physician information booklets.

2. Nine months data deemed by FDA to be acceptable.

XIII. NOMOGRAM CHANGE

Although FDA found the clinical outcomes from the study to be acceptable, the applicant noted overcorrection in eyes with a sphere of less than 2.0 D (with and without hyperopic or mixed astigmatism) and requested subsequent to the study to modify the treatment nomogram. The nomogram used in the clinical trial consisted of adding + 1.0 D to the spherical component of the cycloplegic refraction for all eyes. Because of the noted overcorrection, the amount of spherical correction for eyes with a sphere less than +2.0 D will be the cycloplegic sphere incremented by 50%. This new nomogram has been incorporated into the LADARVision's software and will be the treatment offered by the device.

XIV. FDA DECISION

The applicant satisfactorily addressed FDA's remaining deficiencies. FDA concurred with the above Panel recommendations and implemented all, except for the labeling statement that the risks of refractive instability increase in patients with 2 or more lines loss of BSCVA, since this was not supported by the provided data. CDRH issued an approval order on September 22, 2000.

XV. APPROVAL SPECIFICATIONS

Labeling: Data in the labeling are to be limited to the approved treatment range.

Directions for use: See labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the labeling.

Post-approval Requirements and Restrictions: See approval order.